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REVIEW ARTICLE

Update on Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis: Diagnosis and Management

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Abstract

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are the most severe cutaneous adverse reactions that are typically drug-induced in adults. Both SJS and TEN have high morbidity and mortality rates. SJS/TEN imposes clinical challenges for physicians managing patients suffering from this condition, both because it is rare and because it is a rapidly progressing systemic disease with severe cutaneous, mucosal, and systemic manifestations. Although many cases of SJS/TEN have been reported in the literature, there is no consensus regarding diagnostic criteria or treatment. Significant progress has been made in understanding its genetic predisposition and pathogenesis. This review is intended to provide physicians with a comprehensive but practical SJS/TEN roadmap to guide diagnosis and management. We review data on pathogenesis, reported precipitating factors, presentation, diagnosis, and management SJS/TEN focusing on what is new over the last 5 years.

1 Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) comprise a spectrum of severe cutaneous adverse reactions (SCAR) with life-threatening acute

Key Points

Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a rare, T cell-mediated, severe cutaneous adverse reaction (SCAR) to medication. It is commonly associated with antibiotics and antiepileptics, though a wide array of drugs has been implicated. Mortality rates are high, and the sequelae can be debilitating.

Because SJS/TEN is T cell mediated and is caused by small molecules perturbing the interaction between T cell receptors and peptides presented on MHC molecules, many of the genetic risk factors for SJS/TEN (including some that are clinically actionable) are related to antigen presentation, drug metabolism, and polymorphisms in the MHC complex.

Supportive care remains the mainstay of all SJS/TEN treatment and a high-level evidence base is lacking for any single therapeutic intervention. TNF inhibitors (etanercept), cyclosporine, and combinations of different agents show some promise in unblinded randomized controlled trials and small observational studies.

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effects and serious long-term sequelae. SJS/TEN is a type IV hypersensitivity reaction mediated by an immunologic response to a trigger, most commonly to drugs [1]. Infections may also cause the disease, and some cases remain idiopathic [2–4]. SJS/TEN is characterized by widespread skin and mucosal necrosis [5, 6]. The initial description was named after the physicians Stevens and Johnson in 1922, while the term toxic epidermal necrolysis was introduced by Lyell in 1956 [7]. Notably, the initial description of SJS was most likely post-infectious, and only one of Lyell's handful of initial cases is likely true TEN. The 1993 formal consensus definition classifies cases according to the body surface area (BSA) detached. SJS was defined as < 10% BSA detached, SJS/TEN overlap with 10–30% of BSA detached, and TEN with >30% BSA detached [7]. Although approximately 80% of SJS/TEN cases in adults are medication-associated, in children and young adults, two mimickers, erythema multiforme (EM), and reactive infectious mucocutaneous eruption (RIME; previously known as mycoplasma-induced rash and mucositis or MIRM) are prevalent and should be considered [8]. Immunotherapy used in cancer, like immune checkpoint inhibitors, also are associated with SCAR-like reactions, including SJS/TEN-like reactions, that may be difficult to distinguish from "true" SJS/TEN and often show histopathology more consistent with bullous lichenoid drug eruption or bullous pemphigoid [9–11]. With continued research into immunopathogenesis, it is likely in the future that a more precise classification will be based on molecular markers and histopathological findings.

SJS/TEN has a reported incidence of 1–5 cases per 1,000,000 individuals annually and has a higher incidence in adults than pediatric patients, likely due to increased exposure to potential triggers [6, 12]. However, because SJS shares International Classification of Diseases, Tenth Revision (ICD-10) codes with erythema multiforme, incidence may be overestimated. Furthermore, 36–72% of patients initially diagnosed with SJS/TEN end up having their diagnosis reclassified into a different disease, also contributing to an overestimation of SJS/TEN incidence [13]. Incidence of SJS/TEN also varies by country, partly due to (1) differences in genetic background and (2) differing prescribing patterns [14]. For example, the Han Chinese have a high carrier rate of HLA-B*15:02, an allele strongly associated with carbamazepine-induced SJS/TEN. This association is one explanation for why carbamazepine-induced SJS/TEN has a higher incidence in Southeast Asia than in Europe [15]. Human immunodeficiency virus (HIV) and tuberculosis (TB) endemic locales, like several countries in Africa, also often have higher rates of SJS/TEN owing to an increased use of anti-HIV and anti-TB medications that are high risk for SJS/TEN [16]. Table 1 summarizes known genetic and ethnic associations with SJS/TEN.

Because it causes widespread detachment of skin and mucosal surfaces, SJS/TEN can cause severe complications, including superimposed infection, sepsis, organ dysfunction, and death. Reported mortality rates are as high as 34–50%, with mortality correlating with BSA involvement [1, 5, 12, 17]. In addition, patients with SJS/TEN have a mean loss of life expectancy of approximately 9 years [18]. In addition to morbidity and mortality, expectancy, cost, and readmissions are important to consider in SJS/TEN patients [5, 19]. This review aims to provide an overview and update on the pathogenesis, precipitating factors, presentation, diagnosis, and management of SJS/TEN.

2 Pathogenesis

SJS/TEN is a severe T cell mediated type IV (delayed) hypersensitivity reaction. Over 80% of cases are associated with medication exposure, particularly antimicrobials (sulfa antibiotics), antiepileptics, allopurinol, and nonsteroidal anti-inflammatory drugs (NSAIDs) [20]. More than 300 different drugs and supplements have been implicated [21]. Most cases occur 4–28 days after initial exposure to the drug, though case reports for delayed-onset (6 months) SJS/TEN to lamotrigine and rapid-onset SJS/TEN to acetaminophen and penicillin (3 days) have been reported [22–24]. With rapid onset SJS/TEN, an infectious etiology with protopathic introduction of drugs following first onset of SJS/TEN symptoms should be considered.

The current understanding of SJS/TEN pathogenesis is summarized in Fig. 1. The key event is a tripartite interaction between a peptide presented by a major histocompatibility complex (MHC) on an antigen-presenting cell (APC) and a T cell receptor (TCR) expressed on a CD8+ (cytotoxic) T cell. These drug-reactive T cells may derive from skin-resident memory T cells (T_{RM}) and/or circulating CD8+ T cells [25]. There are many proposed mechanisms by which a drug or reactive metabolite alters a self-protein and activate T cells. In the hapten model and the pro-hapten model, the drug or a metabolite, respectively, covalently modifies the presented peptide, making a previously nonimmunogenic peptide immunogenic. In the pharmacological interaction with immune receptors (p-I) model, the drug noncovalently inserts in the immunological synapse, altering activation. In the altered TCR repertoire or altered peptide model, the drug or its metabolite binds directly to the HLA complex or the TCR (respectively), altering either the peptide repertoire or the confirmation of TCR. Examples of each of these mechanisms have been reported in literature [26].

After the initial interaction, the activated CD8+ T cells trigger downstream cytokine/chemokine production and

Table 1 HLA and ethnic associations with SJS/TEN, adapted from Phillips and Shear, 2024 [140, 141].

Drug	Class	Allele	Ethnic population
Dapsone	Antibiotic/anti-inflammatory	HLA-B*13:01	Southeast Asia (Taiwanese, Thai), Chinese (Han)
Sulfamethoxazole, trimethoprim	Sulfonamide antibiotic	HLA-A*29	Caucasian/European
		HLA-A*11:01	Japanese
		HLA-B12 (HLA-B*44)	Caucasian/European
		HLA-B*38	Caucasian/European
		HLA-B*13:01	Southeast Asia (Taiwanese, Thai, Malaysian)
		HLA-C*08:01	HIV co-infected
		HLA-DR*07	Caucasian/European
Sulfamethoxazole, cotrimoxazole	Sulfonamide antibiotic	HLA-B*13:01	Thai, Taiwanese, Malaysian
		HLA-B*15:02	Thai, Taiwanese, Malaysian
		HLA-B*38:02	Taiwanese, European
Benznidazole	Antiparasitic	HLA-B*35	Bolivian
Carbamazepine	Anticonvulsant	HLA-A*24:02	Chinese (Han)
		HLA-A*31	Japanese
		HLA-A*31:01	Caucasian/European, Chinese (Han), Japanese, Korean
		HLA-B*15:02	Chinese (Han), Indian, Korean, Malaysian, Thai
		HLA-B*15:11	Chinese (Han), Japanese, Korean, Thai, Vietnamese
		HLA-B*15:21	Thai
Lamotrigine	Anticonvulsant	HLA-A*02:07	Thai
		HLA-A*31:01	Korean
		HLA-A*68:01	Caucasian/European
		HLA-B*15:02	Chinese (Han), Thai
		HLA-B*38	Caucasian/European
		HLA-B*58:01	Caucasian/European
		HLA-C*07:18	Caucasian/European
		HLA-DQB1*06:09	Caucasian/European
		HLA-DRB1*13:01	Caucasian/European
Oxcarbazepine	Anticonvulsant	HLA-B*15:02	Chinese (Han)
Phenobarbital	Anticonvulsant	CYP2C19*2	Thai
		HLA-B*51:01	Japanese
Phenytoin	Anticonvulsant	CYP2C9*3	Chinese (Han), Japanese, Malaysian, Thai
		HLA-B*13:01	Chinese (Han)
		HLA-B*15:02	Chinese (Han), Malaysian, Thai
		HLA-B*15:13	Malaysian
		HLA-B*56:02	Thai
		HLA-C*08:01	Chinese (Han)
		HLA-DRB1*16:02	Chinese (Han)
Zonisamide	Anticonvulsant	HLA-A*02:07	Japanese
Nevirapine	Antiretroviral	CYP2B6 T983C	African (Malawian, Ugandan, Mozambican)
		HLA-C*04	African (Malawian)
		HLA-C*04:01 (rs5010528)	African (Sub-Saharan)
Acetazolamide	Carbonic anhydrase inhibitor	HLA-B*59	Korean
Methazolamide	Carbonic anhydrase inhibitor	HLA-B*59	Japanese
		HLA-B*59:01	Chinese (Han), Korean
		HLA-B*55:02	Chinese (Han)
		HLA-C*01:02	Chinese (Han), Korean

Table 1 (continued)

Drug	Class	Allele	Ethnic population
Isoxicam, Piroxicam	Non-steroidal anti-inflammatory	HLA-A*02	Caucasian/European
		HLA-B*12	Caucasian/European
Oxicams	Non-steroidal anti-inflammatory	HLA-B*73	Caucasian/European
Allopurinol	Xanthine oxidase inhibitor	HLA-A*24:02	Korean
		HLA-B*58:01	East Asian, South Asian, Caucasian/European (including Portuguese, Sardinian), Chinese (Han), Japanese, Korean, Thai, Vietnamese
		HLA-C*03:02	Korean
		rs2734583 (BAT1)	Thai, Japanese
		rs3094011 (HCP5)	Japanese
		GA005234 (MICC)	Japanese
		rs3099844	Thai
		rs9263726 (PSORS1C1)	Thai, Japanese
Strontium ranelate	Anti-osteoporotic	HLA-A*33:03	Southeast Asian

epidermal keratinocyte apoptosis through the Fas/Fas ligand (FasL) pathway and TCR/HLA pathway. Keratinocytes likely also trigger apoptosis of other keratinocytes through Fas/FasL signaling, though keratinocyte expression of FasL is controversial [27, 28]. Natural killer (NK) cells can trigger keratinocyte apoptosis through interaction of CD94/NKG2C with HLA-E on keratinocytes and are likely a source of the apoptotic mediator granulysin [29]. Additionally, drug-activated monocytes may trigger necroptosis of keratinocytes via Annexin A1 binding to formyl peptide receptor 1 (FPR1) [30]. Blister fluid collected from SJS/TEN patients has been shown to predominantly contain clonally-expanded CD8+ T cells, in addition to NK cells, monocytes, macrophages, and other immune cells; the fluid also contains several apoptotic mediators, such as TRAIL, perforin, granzyme, TNF-α, soluble FasL, and granulysin [27, 31–36].

Recent work has also suggested a larger role for innate immunity in SJS/TEN pathogenesis, beyond the involvement of NK cells, monocytes, and macrophages. A recent report showed that neutrophils abet inflammation in the early stages of SJS/TEN, by undergoing NETosis and releasing mediators causing necroptosis of keratinocytes [37]. Polymorphisms in toll-like receptor 3 (TLR3), prostaglandin-E receptor 3 (PTGER3), and IKAROS family zinc finger 1 (IKZF1) were associated with cold-medicine-induced ocular SJS/TEN [38]. Chronic-stage ocular SJS/TEN has also shown upregulation in several mediators, including IL-8, IL-6, and interferon-gamma [39].

Because of the importance of MHC to the pathogenesis of SJS/TEN and other drug hypersensitivity reactions, many of the genetic variants most closely linked to the condition are HLA alleles. In particular, HLA-B*15:02 is strongly associated with aromatic anticonvulsant-associated SJS/TEN, with reported odds ratios (OR) for carbamazepine ranging from 17 to 1357 in white and Asian populations [40]. HLA-B genotyping can be considered before prescribing fosphenytoin, phenytoin, oxcarbazepine, and carbamazepine; however, the association has negative predictive value (NPV) significantly less than 100%, particularly in non-East-Asian populations where the association is not as strong [41]. This is in contrast to the absence of the HLA-B*57:01 allele, which has an NPV of 100% for abacavir hypersensitivity (a reaction distinct from SJS/TEN, though illustrative as an example); this reaction previously occurred in approximately 5% of patients receiving the drug, but HLA-B*57:01 screening has eliminated it [42–44]. Similarly, implementation of HLA-B*15:02 screening in Taiwan decreased incidence of carbamazepine-induced SJS/TEN to 0 [45].

A few other genetic risk factors shed light on the pathogenesis of SJS/TEN—polymorphisms in cytochrome P450 and other genes required for drug metabolism, and polymorphisms in the antigen presentation pathway. For example, CYP2C9 and CYP2C19 variants (in particular CYP2C9 poor metabolizer genotypes), are associated with phenytoin-induced SJS/TEN even in the absence of HLA-B*1502 [46, 47]. Another study showed that polymorphisms in the proteasome pathway (required for trimming peptides for presentation on MHC) are associated with SJS/TEN [26, 48]. However, no combination of these variants has 100% NPV, and only a small portion carrying genetic risk factors (2–8%) will develop SJS/TEN. Therefore, further research is needed to better understand these risk factors and effectively use them in a clinical setting.

3 Clinical Presentation

SJS/TEN typically begins within 4 weeks of drug exposure. First symptoms are typically non-specific and precede cutaneous symptoms by a few days in up to one third

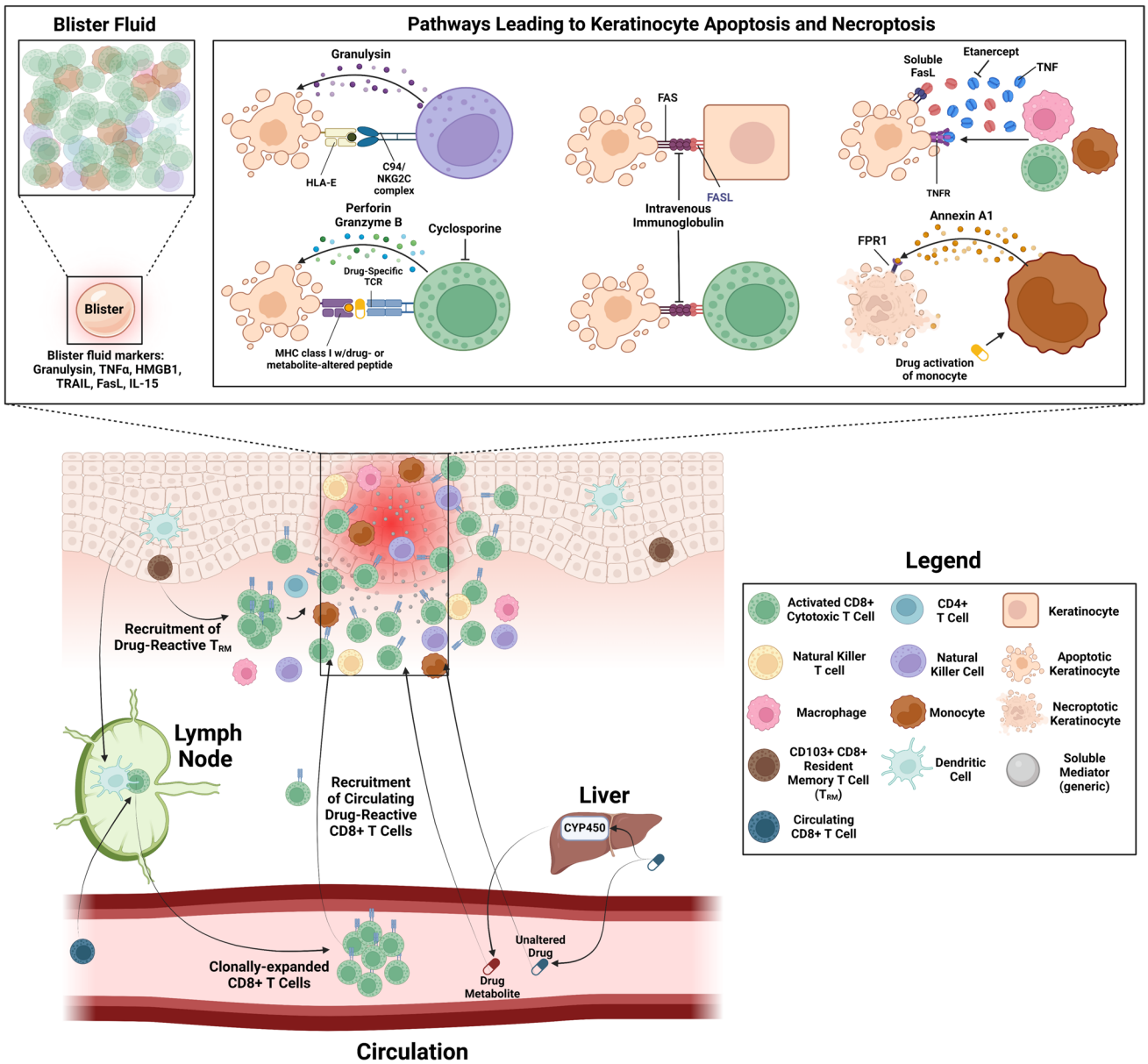

Fig. 1 This figure describes the various pathways that lead to keratinocyte apoptosis and necroptosis, including interactions between antigen-presenting cells (APC), T cells, natural killer cells, monocytes, and keratinocytes. Natural killer (NK) cells can trigger keratinocyte apoptosis through interaction of CD94/NKG2C with HLA-E on keratinocytes and are the likely source of granulysin. APC present a peptide on a major histocompatibility complex (MHC) to a T cell receptor (TCR) expressed on a CD8+ (cytotoxic) T cell. The activated CD8+ T cells then trigger downstream cytokine/chemokine production and epidermal keratinocyte apoptosis through the Fas/Fas ligand (FasL) and the TCR/human leukocyte antigen (HLA) pathways. Additionally, drug-activated monocytes may trigger necroptosis of keratinocytes via Annexin A1 binding to formyl peptide receptor 1 (FPR1). The figure also outlines targets of treatment options including intravenous immunoglobulin, etanercept, and tumor necrosis factor. Abbreviations: TNF = tumor necrosis factor, HMGB1 = high mobility group box 1, TRAIL = TNF-related apoptosis-inducing ligand, FasL = Fas ligand, IL = interleukin, HLA = human leukocyte antigen, CD = cluster of differentiation, NKG2C = natural killer gene 2C, TCR = T cell receptor, MHC = major histocompatibility complex, T_{RM} = skin-resident memory T cells, CYP450 = cytochrome P450. Created with biorender.com

of cases. Early symptoms may include headache, rhinitis, cough, sore throat, or myalgias. At this stage, it is important to have a broad differential, as patients are often misdiagnosed initially. In other cases, mucosal or cutaneous symptoms may be a part of the initial presentation [49, 50].

Over the next few days, cutaneous symptoms begin rapidly. Macular atypical targetoid lesions appear and

often become confluent [51]. These progress to vesicles and bullae, eventually developing into the hallmark full-thickness necrosis, detachment, and skin sloughing [49, 51]. The affected skin is often severely painful [51]. The epithelium of mucosal surfaces, such as the lips, mouth, oropharynx, respiratory tract, gastrointestinal tract, and genitalia, may become necrotic, leading to erosions, ulcerations, and detachment [51, 52]. Ocular involvement is frequent in acute SJS/TEN and may not become apparent until the more chronic stages [53]. Ocular complications of SJS/TEN are broad including, chronic dry eyes, corneal inflammation, trichiasis, symblepharon, and lid margin keratinization [53]. Dysosmia and dysgeusia have also been reported as complications of mucosal involvement in SJS/TEN [54]. Examples of cutaneous, ocular, genital, and oral involvement are shown in Fig. 2.

Systemic organ involvement can occur in SJS/TEN through a variety of mechanisms. Epidermal barrier breakdown can lead to homeostatic dysfunction, electrolyte derangement, hypothermia, dehydration, and/or sepsis. Organs with an epithelial lining can be directly affected, leading to respiratory distress syndrome, colitis, pancreatic injury, liver dysfunction, and other complications [27, 51, 55]. Cross-reactivity to bone marrow antigens may cause pancytopenia in some patients [56].

4 Clinical Assessment

Red flags on initial examination include skin pain, prodromal symptoms and mucositis in relation to a rapidly developing extensive rash. On presentation, a thorough skin examination should be conducted to evaluate the extent of cutaneous involvement, along with examination by ophthalmology, urology, and gynecology specialists for mucosal involvement. Skin, ocular, and oral examinations should be conducted daily. Patients should also be closely examined and monitored for systemic involvement [57]. Laboratory assessment including complete blood count, a comprehensive metabolic panel to assess electrolyte status in the setting of significant insensible losses, and baseline arterial blood gas to determine respiratory status are essential on initial evaluation. Additionally, electrolytes, glucose, and fluid balance should be monitored daily during admission and managed appropriately [58]. Imaging should be obtained if clinically indicated. Given the high prevalence of oral and mucosal involvement, it is also critical to evaluate if there is a need for orotracheal intubation [59].

4.1 Diagnosis

There are no standard diagnostic criteria for SJS/TEN, though the presence of macular targetoid lesions, involvement of two mucous membranes, recent drug exposure, and

Fig. 2 Images of SJS/TEN. SJS/TEN presents with desquamation (**A**) and bullae (**B**) over large areas of skin. Additionally, it can present with genital (**C**), oral (**D**), and ocular (**E**) involvement. The condition often heals with persistent dyspigmentation (**F**)

corresponding histopathology are all suggestive. As defined in the introduction, the clinical differentiation between SJS and TEN is based on body surface area involvement specifically of detached or detachable skin. Other lesions that may appear on intact skin (and thus do not count towards BSA involvement), include morbilliform rash, erythematous macules or patches, purpura, and targetoid lesions. SJS is when < 10% BSA is affected, SJS-TEN overlap is 10%–30% BSA, and TEN is > 30% BSA [60].

Clinical features of SJS/TEN can mimic other dermatologic diseases, including erythema multiforme, reactive infectious mucocutaneous eruption, generalized bullous fixed drug eruption, staphylococcal scalded skin syndrome, pemphigus vulgaris, and acute graft versus host disease, among others (Table 2). It is important to differentiate between these conditions, as they have different treatments and prognoses. In particular, note that Nikolsky sign is not pathognomonic for SJS/TEN alone, as it can be present in multiple diseases [61].

Histologic features of SJS/TEN include full thickness epidermal necrosis, keratinocyte apoptosis, basal vacuolar change, subepidermal bullae, subepidermal clefting, and mild T cell infiltrate [62–64]. Drug-induced SJS/TEN skin biopsies (versus infection or immunization-induced) may have a dermal infiltrate with a high number or eosinophils or neutrophils [64]. Histologic findings may also be indicative of severity of disease or worse prognosis; for example, skin biopsies from patients with TEN (versus SJS) may have a more significant dense dermal mononuclear infiltrate [65]. New research has supported that ex vivo confocal laser scanning microscopy may serve as a safe, rapid, non-invasive alternative to skin biopsy, though this is not yet widely available [66].

Historically, erythema multiforme major (EMM) has been particularly difficult to differentiate from SJS/TEN [67]. There are various diagnostic tests that can assist. EM generally is typically characteristic by the appearance of both macular and papular typical targetoid lesions (with three zones of color, as opposed to atypical targetoid lesions which have two) and papular atypical targetoid lesions, all of which are generally absent in SJS/TEN which only has macular atypical targetoid lesions [68]. Immunohistochemistry for cytotoxic molecules (such as granulysin, perforin, and granzyme B), CD4 and Treg can help differentiate SJS/TEN from EMM [69]. Demographics (with EMM skewing younger) and risk factors (drug exposure for SJS/TEN versus respiratory infection for EMM) should also be considered [70]. Direct immunofluorescence (DIF) and enzyme-linked immunosorbent assay (ELISA) are important to rule out autoimmune bullous disease, severe cases of which can mimic SJS/TEN [63, 71, 72].

Much recent research has focused on biomarkers for SJS/TEN diagnosis and prognostication. Granulysin is a cytotoxic mediator involved in keratinocyte death and is highly expressed in SJS/TEN blister fluid and serum [31, 73, 74]. Blister fluid and serum granulysin concentration have been found to have a linear relationship with BSA involvement [31, 75]. Serum granulysin has a sensitivity of 80% and specificity of 95.7% for early diagnosis of SJS/TEN in patients with nonspecific drug rash, and a rapid immunochromatographic test strip for granulysin has been developed, though is not yet widely available [76]. Serum granulysin may also be used as a predictor of SJS/TEN development 2–4 days prior to skin detachment or development of mucosal lesions ($p < 0.010$) [73]. It is, however, important to note that granulysin has also been detected on histopathology in the inflammatory infiltrate patients with other cutaneous adverse drug reactions including drug reaction with eosinophilia and systemic symptoms (DRESS) and fixed drug eruption [77]. Furthermore, granulysin has not been validated in large cohorts and thus has not been widely adopted in clinical settings. Other biomarkers (IL-15, HMGB1, IL-13, etc.) have also been studied, but none are currently considered standard-of-care [78–80].

HLA testing has a role in risk stratification of patient populations as an option prior to starting SJS/TEN culprit drugs. Several studies have estimated positive predictive value (PPV) and NPV of HLA testing for patients who develop SJS/TEN, which tend to differ by ethnic group [81]. Understanding HLA associations with drugs implicated in the development of SJS/TEN can help with avoidance of a particular drug and/or knowledge to prevent re-exposure if the patient is an SJS/TEN survivor.

4.2 Determination of Causality

Determining causality is critical for prompt discontinuation of the culprit drug and strict avoidance of the culprit drug and potentially cross-reactive drugs in the future [82]. Causality is primarily determined through careful history-taking and construction of a drug timeline, including prescription drugs, over-the-counter medications, and supplements. Determining when each drug was started, stopped, held, or had a dose change is critical. It is also important to consider whether the patient has a history of cutaneous adverse reactions to medications or has underlying comorbidities, such as cancer or HIV.

Multiple algorithms have been developed to assist with the determination of drug causality, including the algorithm of drug causality for epidermal necrolysis (ALDEN), the Liverpool Causality Assessment Tool, and the Naranjo scale [82, 83]. The ALDEN score is considered the gold-standard;

Table 2 Differential diagnoses to consider when evaluating a patient with SJS/TEN symptoms

Differential diagnosis	Lag time	Prodrome	Characteristic findings	Systemic symptoms	Trigger(s)/pathogenesis	Histology
SJS/TEN [49]	4–28 days	Fever, malaise	Skin pain, Nikolsky sign	Yes	Drug, infection, or idiopathic	Full-thickness keratinocyte necrosis
Generalized bullous fixed drug eruption [142]	30 min to 48 hours	None	Same site recurrence with progression each time the drug is ingested; postinflammatory hyperpigmentation lasting weeks to months	No	Drug, prior exposure required	Vacuolar interface dermatitis with both superficial and deep perivascular infiltration of eosinophils and lymphocytes, individual necrotic keratinocytes, and pigment incontinence
Staphylococcal scalded skin syndrome [143]	24–48 hours	Irritability, fever, and malaise	Erythema and fissures in flexural areas, followed by blisters. Periocular and periorificial crusting and radial fissuring.	Yes	*Staphylococcus aureus* infection	Epidermal cleavage at or below the stratum granulosum, indistinguishable from pemphigus foliaceus
Erythema multiforme major [144, 145]	7–10 days	Fever	Typical target lesions	Occasionally	Mostly infection	Vacuolar interface dermatitis, lymphocytic infiltration at the dermo-epidermal junction
Reactive infectious mucocutaneous eruption (RIME) [146]	1 week	Cough, fever, myalgia, rhinitis	Vesiculobullous lesions and atypical targetoid lesions	No	Infection	Toxic epidermal necrosis-like pattern with keratinocyte apoptosis
Drug reaction with eosinophilia and systemic symptoms (DRESS) [147]	4–8 weeks	Fever, malaise	Facial edema, lymphadenopathy, and typically morbilliform rash, but any type of skin involvement is possible	Yes	Drug + viral infection	Varied, may include basal squamatization, dermal red blood cell extravasation, or interface inflammation
Acute generalized exanthematous pustulosis (AGEP) [148]	Antibiotics: 1 day Other drugs: 11 days	Fever, malaise, leukocytosis	Edematous erythema in large skinfolds, then widespread; followed by the development of multiple pinpoint, nonfollicular, sterile pustules and desquamation	Yes	Mostly drug, but also infection, vaccination, ingestion, spider bites	Intracorneal, subcorneal, and/or intraepidermal pustules with papillary dermal edema and both neutrophilic and eosinophilic perivascular and interstitial infiltrate
Immune checkpoint inhibitors SJS/TEN-like reactions [63]	Weeks to months	Fever, sore throat, malaise	Non-pruritic truncal morbilliform rash	No	Drug reaction	Full-thickness keratinocyte necrosis, subepidermal clefting
Pemphigus vulgaris [71]	N/A	None	Painful blisters and erosions affecting the skin and mucous membranes	Yes	Autoimmune	Intraepidermal blistering with suprabasal epidermal acantholysis, positive direct immunofluorescence for intracellular deposition in the epidermis

Table 2 (continued)

Differential diagnosis	Lag time	Prodrome	Characteristic findings	Systemic symptoms	Trigger(s)/pathogenesis	Histology
TEN-like lupus erythematosus [149]	N/A	None	Nikolsky sign	Yes	Autoimmune	Epidermal necrosis with lupus band on direct immunofluorescence, with possible bullae
Rowell syndrome [150–152]	N/A	None	Lupus erythematosus with erythema multiforme-like target lesions	Yes	Autoimmune	Vacuolar interface dermatitis, lymphocytic inflammatory infiltrate, negative direct immunofluorescence, can have necrotic keratinocytes
Severe allergic or irritant contact dermatitis [153]	1–3 days	None	Prominent epidermal involvement. Pruritic papules, plaques, and/or vesicles	Occasionally	Local substance (irritant or allergic)	Spongiosis, dermal edema, and inflammatory infiltrate mostly eosinophils
Acute graft versus host reaction [154]	Days to 6 months	Nausea, abdominal pain	Maculopapular lesions, sclerosis	Yes	Autoimmune	Vacuolar interface dermatitis, necrotic keratinocytes

it ranges from −12 to 10, and is determined by six factors—the time between drug initiation and onset of symptoms, the half-life of the drug, whether the patient had previously taken the drug (prechallenge), whether the drug was continued beyond the progression phase of the disease (dechallenge), drug notoriety, and other possible alternatives [84]. Comparing patient history with ALDEN scores has revealed correlations with other medical conditions that potentially increase the risk of SJS/TEN, such as psoriasis, history of drug reactions or allergies, systemic lupus erythematosus, malignancy, and diabetes mellitus [83]. In contrast, the Naranjo score ranges from −4 to 13, and consists of ten questions. Unlike ALDEN, the Naranjo score accounts for confirmation by objective evidence, detection of the drug in blood, and whether the reaction reappeared with placebo or readministration [85]. The Liverpool algorithm was developed from the Naranjo scale, due to several questions in the latter often having answers of "unknown" or "unable to assess" [86].

Determining drug causality after the fact is also an important area of research. Post-hoc testing methods include ex vivo/in vitro methods, such as lymphocyte transformation testing (LTT), ELIspot, and cytokine release assays, and in vivo methods, such as epicutaneous patch testing (PT) [87]. Intradermal ("prick") testing (IDT) has not been recommended owing to the theoretical risk of reproducing the original reaction [88]. However, skin testing (both PT and IDT) for SJS/TEN has low sensitivity. In a systematic review, reported positivity rates for PT ranged from 13 to 33% (which increases to 54–77% for focused testing to suspected medication) [89, 90]. This varies widely by drug—allopurinol (and its metabolite, oxypurinol, thought to be causative) is usually negative, with a sensitivity of 0%, while antiepileptics and antibiotics are positive more frequently [89, 91]. In general, patch testing seems to have much greater utility in other types of severe cutaneous adverse reactions, like DRESS, acute generalized exanthematous pustulosis (AGEP), and morbilliform drug eruption (MDE), than SJS/TEN [92, 93]. Partly because of this low sensitivity, patch testing has not been widely adopted, and more large-scale studies are needed.

Several culture-based assays, in which patients' peripheral blood mononuclear cells (PBMC) are co-cultured with suspected medication, have also been developed. In LTT, cultured cells are assayed for proliferation. Other assays measure cytokines in cell culture, detecting intracellular apoptotic mediators by flow cytometry, or detect the release of mediators, such as granzyme from individual cells via ELIspot [88, 94]. While LTT alone has low sensitivity, combining multiple assays together can increase the sensitivity substantially (in one study up to 80%) [94–96]. Of note, these assays are not commercially available and as a result, their use is limited.

4.3 Severity Assessment

Given that SJS/TEN has a high mortality rate, estimated to be between 34 and 50% globally, the most critical clinical assessments are severity and mortality risk [97, 98]. Severity and mortality risk of SJS/TEN can be estimated with several validated tools, including the Score of Toxic Epidermal Necrolysis (SCORTEN); the revision of SCORTEN (Re-SCORTEN); the age, bicarbonate, cancer, dialysis, and 10% body surface area risk model (ABCD-10); and the clinical risk score for toxic epidermal necrolysis (CRISTEN).

SCORTEN is well-established as a method to determine mortality risk [12]. SCORTEN utilizes the following seven clinical indicators: age $\geq$ 40 years, active cancer, heart rate $\geq$ 120 beats per min, serum blood urea nitrogen > 28 mg/dL, detached or compromised body surface $\geq$ 10%, serum bicarbonate < 20 mmol/L, and serum glucose > 250 mg/dL [7, 99, 100]. SCORTEN should be calculated on day 1 and 3 of hospitalization and is used to score severity and estimate mortality by using the above variables to calculate probability of death [7].

Koh et al. proposed a revision of SCORTEN (Re-SCORTEN) for mortality prognostication, adding the red blood cell distribution width to hemoglobin ratio (RHR), which can be determined from a basic complete blood count. The authors incorporated RHR into SCORTEN by adding a value of 2 for patients with RHR > 1.19, which led to significantly increased prognostic accuracy [101].

ABCD-10 is a risk prediction model for severity and mortality that uses five indicators (age $\geq$ 50 years, body surface area > 10%, serum bicarbonate < 20 mmol/L, active cancer, and prior dialysis) [100, 102]. This differs from SCORTEN by increasing the weight of cancer on prognosis and by including history of prior dialysis instead of only current kidney function [102]. However, this model has been found to be inferior to SCORTEN at mortality prediction [103].

CRISTEN is a novel risk prediction model of SJS/TEN to predict severity and mortality that uses ten clinical parameters (without the immediate need for laboratory values): age > 65 years; epidermal detachment > 10% of BSA; active cancer; diabetes mellitus on treatment with medication; chronic kidney disease; bacterial infection including pneumonia, sepsis, or urinary tract infection; cardiac disease including hypertension under treatment; antibiotics in the list of culprit drugs; mucosal damage affecting ocular, buccal, and genital mucosa; and recent systemic corticosteroid therapy before the onset of SJS/TEN [104]. The benefit of CRISTEN is that it does not require laboratory testing prior to prediction of mortality, which may improve versatility and promptness; rather, it uses clinical features. The validation study did have a lower area under the curve than the creation study ($p > 0.05$); however, it may be more beneficial to utilize this scoring system as an adjunct to SCORTEN for early prognostication [104].

Many SJS/TEN scoring systems are prognostic models and do not allow for dynamic assessment or incorporate cutaneous morphology traits. A recent Delphi consensus exercise redefined morphology and distribution terminology for TEN and reinforced the need for developing a skin-directed and morphologically based SJS/TEN scoring system [105]. There are additional scoring assessments that are available, such as time to partial re-epithelialization, time to complete re-epithelialization, and BSA involved, among others; however, use should be discouraged until these are validated [100].

Beyond validated scores, a few laboratory values have emerged as potential markers of severity. These include lactate dehydrogenase, creatine kinase, granulysin, and interleukin-15, all four of which correlate directly with BSA involvement [73, 75, 106, 107]. There is also evidence that a positive anti-SS-A serology ay predict worse outcomes and therefore may prompt more aggressive treatment [108]. While these studies are limited, it is a promising opportunity for further research and may become useful for clinical practice to predict severity early in the disease process.

5 Treatments

5.1 Supportive Care

Treatment for SJS/TEN is complex, and there are no standardized guidelines for treatment currently. Our inability to accurately measure severity and appropriate outcomes is a major hindrance to determining standard of care. Withdrawal of the offending drug and all nonessential medications is critical, followed by hospitalization and supportive care. Furthermore, owing to the potential of multi-organ involvement, multidisciplinary care is often required [109–112].

Depending on the severity, the patient may be transferred to a burn center or intensive care unit [60]. Aggressive supportive care is the mainstay of initial management, and should include wound care, oral care, ocular care, genitourinary care, pain management, airway management, fluid and electrolyte management, stress ulcer prophylaxis, nutrition management, and deep vein thrombosis prophylaxis [58].

A particularly important consideration in SJS/TEN is the prevention of sepsis, which is the major cause of mortality in these patients [113]. Maintenance of an aseptic environment is critical and careful septic handling is required. Some advocate aggressive surgical debridement, particularly for TEN, to remove necrotic skin as a potential source of infection, while others advocate conservative management with anti-shear measures, leaving devitalized skin intact to function as a natural bandage; there is currently no consensus,

and both approaches have shown equivalent re-epithelialization rates [114]. Close monitoring of body temperature and hemodynamic status, along with frequent culture of skin, urine, and blood specimens for bacteria and fungi is warranted. While prophylactic antibiotics are not recommended as part of usual supportive care, prompt use of antibiotics in the setting of clinical infection is likely critical.

5.2 Systemic Treatment

There is no high-level evidence for the treatment of SJS/TEN; the available studies include two open randomized controlled trials (RCT) and several small observational studies, case series, or retrospective reviews. Medications that have been reported to have some benefit are summarized in Table 3.

Cyclosporine, used on the basis of its T cell-specific mechanism, shows promise as an immunomodulatory medication that in small observational studies has had positive impact on hospital stay and progression of skin detachments in SJS/TEN patients [49, 115–117]. However, cyclosporine can be nephrotoxic and is avoided in patients who have a kidney injury, as kidney function is a critical component of SCORTEN and ABCD-10 prognoses.

Oral and intravenous corticosteroids are often used. Studies have suggested that prompt initiation of high dose corticosteroids within 1–2 days of symptoms onset leads to improved outcomes [118, 119]. However, other evidence suggests that the use of corticosteroids is associated with increased risk of infection [120]. Intravenous immunoglobulin (IVIG), which likely works via inhibition of the Fas receptor, has been used both alone and in combination with corticosteroids [28]. A network meta-analysis published in 2021 showed that corticosteroid/IVIG combination therapy was the only with a mortality benefit compared to control [121]. However, many studies suggest limited benefit to IVIG, and it could be harmful in those with renal impairment [122–124]. It is likely for such treatment including IVIG and corticosteroids that the time window to initiation to achieve a beneficial effect is very short to be feasible in clinical practice.

Biologic TNF-α inhibitors, such as etanercept, have been shown to be an effective treatment with minimal side effects [74, 125–129]. In a 2022 Cochrane review, etanercept twice weekly until healing was the only treatment that reached low-certainty evidence, possibly offering a superior mortality benefit to corticosteroids [130]. Patients treated with TNF-α inhibitors have achieved complete skin re-epithelialization and in a shorter prior of time than patients treated with other treatments such as corticosteroids [49]. A randomized, controlled open-labelled trial comparing intravenous corticosteroids to etanercept showed a significant decrease in time to re-epithelialization [74]. Interestingly the combination of etanercept and other treatments may show benefit—a multicenter retrospective study showed that the combination of etanercept and corticosteroids showed improved mortality rates compared with the combination of corticosteroids/IVIG and corticosteroids alone [131].

Special populations, such as pregnant patients and children who may require additional considerations and treatment modifications. For example, when treating a pregnant woman with SJS/TEN, careful consideration regarding fetal status, delivery method, and whether the disease has affected the fetus must be considered [49].

6 Chronic Complications and Care of the SJS/TEN Survivor

Patients with SJS/TEN may suffer from numerous chronic complications (Table 4). As during the acute illness, multidisciplinary follow up care is also recommended upon

Table 3 Systemic treatment options for SJS/TEN.

Treatment	Recommended dosage
Cyclosporine* (PO) [116, 117]	3–5 mg/kg/d q12 h for 2 weeks with gradual taper
Etanercept* (SC) [74, 128, 129]	25 mg SC injection or 50 mg if > 65 kg twice weekly until re-epithelialization
Corticosteroids* (IV) [155–157]	Dexamethasone 1.5 mg/kg/day for three days Prednisolone 60–250 mg/day for 2 to 12 days Methylprednisolone 250–1000 mg/day for three days
Intravenous immunoglobulin** (IV) [116, 158, 159]	4 g/kg divided over 3 days OR 0.75 g/kg/d for 4 days OR 1 g/kg/d for 3 days

*Combination therapy has been reported among these interventions

**Controversial use, recommended in combination with corticosteroids and/or plasmapheresis

Abbreviations: PO = oral, IV = intravenous, SC = subcutaneous

Table 4 Long-term complications of SJS/TEN [18, 53, 133, 134, 160–163].

General
Fatigue
Malaise
Sleep problems
Chronic pain
Psychiatric
Depression
Anxiety
Post-traumatic stress disorder
Dysthymia
Cutaneous
Dyspigmentation
Pruritus
Photosensitivity
Abnormal sweating
Eruptive nevi
Cutaneous scars
Postinflammatory skin changes
Nail loss
Hair loss
Ocular
Dry eyes
Symblepharon
Eyelid dysfunction
Chronic ocular surface inflammation
Opacification
Conjunctivalization
Keratinization
Neovascularization
Punctal damage and tear duct scarring
Pain
Photophobia
Visual impairment (i.e., loss of acuity)
Oral mucous membrane
Dryness
Dental caries
Abnormal root development
Hypoplasia of permanent teeth
Ulceration and synechiae
Mucosal scarring
Permanent loss of tongue papillae/dysgeusia
Dysosmia
Otorhinolaryngologic
Hypopharyngeal stenosis and impaired swallowing
Pharyngeal-bronchial fistula formation and recurrent aspiration
Dysphonia
Otalgia
Tinnitus
External auditory canal stenosis
Nasal septal synechiae
Pulmonary
Dyspnea
Cough
Wheezing
Obstructive lung disease (i.e., bronchiolitis obliterans, bronchiectasis, chronic obliterative bronchitis)
Gastrointestinal
Esophageal stricture or webs
Dysphagia
Intestinal ulcers
Malabsorption (secondary to duodenal villi destruction)
Diarrhea
Gynecologic/Genitourinary
Vulvar pain/dyspareunia
Vulvar and vaginal adenosis or stenosis
Labial fusion
Hematocolpos and hydrocolpos (secondary to complete vaginal fusion)
Subfertility or infertility (secondary to menstrual abnormalities)
Urethral erosions and strictures
Balanitis
Phimosis

Of note, studies have reported that hepatic and renal complications are thought to be the result of drug hepatotoxicity and nephrotoxicity rather than a direct result of SJS/TEN disease state, so these were excluded from our table

discharge to monitor for sequelae that impact quality of life. Dental/oral, ocular, genital, and psychological sequelae are common [132].

Survivors of SJS/TEN experience tremendous psychosocial effects that are often underreported. It is important to screen patients with SJS/TEN during hospitalization and in the follow-up period for psychiatric illnesses [133]. Survivors report high rates of post-traumatic stress disorder, depression, and anxiety [134, 135]. Physicians may utilize validated questionaries to screen survivors for psychiatric status, such as Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 (GAD-7), and Primary Care Post-Traumatic Stress Disorder Screen (PC-PTSD) [134]. Given the complex nature of chronic complications, particularly psychosocial, there are many support groups for survivors located internationally (Table 5).

In addition to an increased rate of psychosocial effects, SJS/TEN survivors have an estimated reduced life expectancy of about 9 years and an increased risk of ensuing higher healthcare-related costs [136, 137]. The decreased life expectancy may be owing to a reduced and delayed usage of high-risk drugs that may be associated with SJS/TEN. Often, survivors are left avoiding multiple

Table 5 SJS/TEN support groups and patient organizations

Support group/patient organization	Website	Contact details
SJS/TEN Support Hotline	N/A	+1 (385) 244-0987
SJS Canada	https://www.sjscanada.org	info@sjscanada.org
SJS Foundation	https://sjsupport.org/	sjsfoundation@sjssupport.org
SJS Awareness Oregon	https://www.sjsawarenessoregon.org/	OregonSjs@gmail.com
SJS Kids Support	https://www.sjskidsupport.org/	sjsupport@gmail.com
Amalyste	https://www.amalyste.fr/	entraide@amalyste.fr
SJS Awareness UK	https://www.sjsawareness.org.uk	info@sjsawareness.org.uk
Kindness for Kimberlee	https://www.kindnessforkimberlee.org/	https://www.kindnessforkimberlee.org/contactus

medications if the SJS/TEN trigger was not clearly identified. In situations where use of a medication is necessary and alternatives are not available, there can be shared decision making with the patient to consider a drug challenge test in unique scenarios [138]. Genetic screening can be done prior to use, but this may lead to a delay in treatment [18, 136].

Professor Jean-Claude Roujeau, one of the most important leaders of SJS/TEN, suggested three key objectives when supporting SJS/TEN survivors: (1) carefully listen to patients concerns and collaborate with them to treat psychosocial distress, (2) advance clinical and basic research to better understand SJS/TEN long-term sequalae, and (3) ensure patients have equitable access to health care, and consider if patients can earn compensation in some capacity. Given the high mortality rate of patients with SJS/TEN, Professor Jean-Claude Roujeau advocated for affected patients to be termed true "victims" [139].

7 Conclusion and Future Directions

This review aims to provide an overview and update on the pathogenesis, reported precipitating factors, genetic risk factors, presentation, diagnosis, and management of SJS/TEN. Important areas of further study include continued elucidation of immunopathogenesis and genetic associations, investigation into potential biomarkers to aid in diagnosis and prognostication, and standardization of optimal treatment. These advances will allow for superior preventative screening, diagnosis, and management of SJS/TEN.

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Declarations

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